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Large-Scale Synthesis of (*R*)-2-Amino-1-(2-furyl)ethanol via a Chemoenzymatic Approach

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Abstract:

A two-step chemoenzymatic synthesis of (*R*)-2-amino-1-(2-furyl)ethanol for laboratory production was developed followed by successful up-scaling to kilogram scale. The generation of the asymmetric centre was accomplished by a highly enantioselective cyanohydrin reaction of furan-2-carbaldehyde with hydrocyanic acid catalyzed by the hydroxynitrile lyase from *Hevea brasiliensis*. Subsequent sodium borohydride reduction furnished the desired product with an enantiomeric excess of higher than 99.5%. This procedure can be considered a convenient general route for the stereoselective synthesis of ethanol amine derivatives underlining the role of biocatalysis for the generation of stereogenic centres in the synthesis of chiral intermediates.

Introduction

The demand for chiral enantiopure advanced intermediates for the pharmaceutical industry is constantly increasing.[1] As a consequence, the development of convenient protocols for the production of single enantiomers of chiral materials has become a very important issue.[2]

A recent research project at DSM was dealing with the synthesis of (*R*)-2-amino-1-(2-furyl)ethanol (**3**) on kilogram scale.

The 1,2-amino alcohol moiety is a widespread structural motif in natural and synthetic biologically active molecules. Therefore, these intermediates are important building blocks for fine chemical synthesis owing to the biological significance of these substances.[3] To date a wealth of synthetic procedures for the production of vicinal amino alcohols has been developed.[4] Obvious synthetic strategies to obtain **3** comprise—among others—the opening of the corresponding enantiopure epoxide and the stereoselective reduction of a corresponding ketone.[5]

In our development efforts we needed to set up a short and efficient sequence for the production of **3**, possibly involving the generation of the chiral centre in a single stereoselective step to avoid the resolution of a racemate. In general the application of a robust and reliable in-house technology for the synthesis of newly emerging target molecules appears to be an appealing strategy for synthetic planning. In this regard we envisaged the route to vicinal amino alcohols via the reduction of cyanohydrins, which is supposed to be especially attractive for the synthesis of amino alcohols containing a primary amine function.

The synthesis of the desired (*R*)-cyanohydrin has been reported in the literature either by dipeptide-catalyzed hydrocyanation,[6] metal-mediated cyanosilylation,[7] kinetic resolution[8] or hydroxynitrile lyase-catalyzed hydrocyanation.[9] The asymmetric enzymatic large-scale production of cyanohydrins catalyzed by both (*R*)- and (*S*)-hydroxynitrile lyases is well established at DSM,[10] and the synthesis of a large number of enantiomerically enriched cynohydrins has been reported in the literature.[11] Hydroxynitrile lyases are versatile plant enzymes which catalyze the cleavage of α-hydroxynitriles to set free HCN in a vegetal defense mechanism.[12] The reversed process—the stereoselective addition of hydrocyanic acid to carbonyl compounds—has matured to a very powerful tool in enzymatic asymmetric organic synthesis.[13] To date these biocatalysts are available in recombinant form for the production of enantiomerically enriched cyanohydrins

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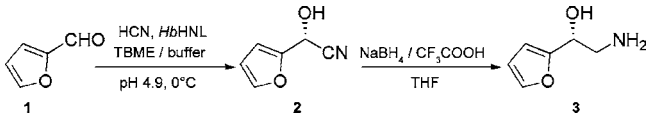
Scheme 1. **Chemoenzymatic approach for the production of (*R*)-2-amino-1-(2-furyl)ethanol (3)**



with both (*R*)- and (*S*)-configuration, rendering this technology enantiocomplementary.[10,14]

Herein we report on the synthesis of (*R*)-2-amino-1-(2-furyl)ethanol (**3**) via (*R*)-2-(2-furyl)-2-hydroxyacetonitrile (**2**) by stereoselective enzyme-catalyzed hydrocyanation of furan-2-carbaldehyde (**1**) using the recombinant hydroxynitrile lyase from *Hevea brasiliensis* (*Hb*HNL) followed by reduction of the cyanohydrin **2** with sodium borohydride. This procedure enables the use of a reliable in-house technology for the stereoselective generation of the asymmetric centre in the key step of a straightforward synthesis, applying furan-2-carbaldehyde (**1**) as a cheap starting material and avoiding any protection/deprotection steps (Scheme 1).

Results and Discussion

Synthesis of (*R*)-2-(2-Furyl)-2-hydroxyacetonitrile (2) on Laboratory Scale. The first task of the project was to synthesize a 100-g sample of **3** with an enantiomeric excess greater than 98%. At the same time it was imperative to choose the reaction conditions in such a way that would allow up-scaling of the procedure.

To minimize the time for the development of the process the hydroxynitrile lyase from *Hevea* brasiliensis (*Hb*HNL) was the enzyme of choice to be investigated for the carboligation step to yield the cyanohydrin intermediate **2**, not only because of its stereopreference and substrate range but also because we were able to rely on a wealth of experience from prior applications of this enzyme.

Furthermore, the enzyme is produced by overexpression and is purified at DSM, thus providing sufficient quantities of biocatalyst for development and production. The *Hb*HNL-catalyzed addition of HCN to furan-2-carbaldehyde (**1**) was carried out in an aqueous buffer/*tert*-butyl methyl ether (TBME) emulsion at pH 5.2 and 0 °C. In previous comprehensive studies ethers such as diisopropyl ether and TBME proved to be the most suitable solvents for this purpose. The choice of pH for enzymatic cyanohydrin reactions is of utmost importance. At low pH (<5) the spontaneous unselective addition of HCN to the carbonyl substrate and racemization of the cyanohydrin product are suppressed. At the same time the enzyme activity is strongly reduced, or even complete inactivation of the catalyst is observed. The application of higher pH values (6−7) provides optimal biocatalyst activity. However, this is usually accompanied by a decrease of enantiomeric excess of the product due to nonenzymatic HCN addition. Freshly produced hydrocyanic acid as the cyanide source was added dropwise to the reaction mixture over a period of 15 min. After completion of the reaction (prolonged reaction times lead to a decrease of enantiomeric excess) and product isolation, the cyanohydrin was analyzed by chiral GC after acetylation using racemic material as a reference. Due to internal laboratory safety regulations limiting the amount of HCN applied in one transformation, the required quantity of **2** had to be synthesized in cumulative batches. In every single reaction the product was obtained in 83−95% yield with an optical purity exceeding 99%. In total, 290 g of **2** were produced in reproducible constant yield and quality in nine single batches (Table 1). In general a reuse of the biocatalyst in successive batches is possible and economically feasible; however, recycling of the enzyme was not considered on this production scale.

***Table 1. Hb*HNL-catalyzed synthesis of (*R*)-2-(2-furyl)-2-hydroxyacetonitrile (2)**

batch	quantity [g]	yield [%]	ee [%]	batch	quantity [g]	yield [%]	ee [%]
1	32.4	88	99.7	6	31.3	85	99.6
2	33.3	90	99.6	7	30.4	82	99.6
3	33.7	91	99.6	8	30.8	83	99.6
4	32.0	87	99.8	9	31.3	85	99.8
5	35.0	95	99.6				

It is important to note that the orientation of asymmetric induction of the (*S*)-selective *Hb*HNL is maintained with furan-2-carbaldehyde as the substrate. The (*R*)-configuration of **3** has to be assigned according to the Cahn−Ingold−Prelog rules.

Reduction of (*R*)-2-(2-Furyl)-2-hydroxyacetonitrile (2). The reduction of α-hydroxynitriles to yield vicinal amino alcohols is conveniently accomplished with complex metal hydrides, e.g., lithium aluminium hydride (LAH) or sodium borohydride. This particular transformation is reported to proceed without racemization which was a fundamental prerequisite for our purposes.[15] Owing to the hazardous nature of LAH—especially with regard to large-scale application—and its elevated price compared to $NaBH_4$, we considered the latter the reagent of choice for the reduction of **2**. Hence, we elaborated this transformation by applying $NaBH_4$ in THF in combination with a carboxylic acid (to generate the borane−THF complex) followed by aqueous quench of the reaction. After acidifying the aqueous layer and extraction with an organic solvent, **3** was purified by crystallization.

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However, the reduction step required more optimization work than the HCN addition. Trifluoroacetic acid turned out to be the appropriate acid component to give product **3** in 64% yield. Replacing trifluoroacetic acid with trichloroacetic acid (mainly for cost reasons) furnished **3** in only 37% yield, although the conversion was virtually identical in both cases, implying that trichloroacetic acid was not compatible with the workup procedure (vide infra). After the addition of water to decompose excess $NaBH_4$ the reaction mixture was filtrated, THF was removed, and the remaining aqueous phase was acidified. At this stage careful control of the pH is mandatory since product degradation was observed at pH 1. The formation of a precipitate during the decomposition of the $NaBH_4$ excess can be avoided by adding 1 M sulphuric acid instead of water to the reaction. Stirring in alkaline solution by addition of a 5 N sodium hydroxide solution at elevated temperature (60 °C) after quench of the reaction mixture turned out to be another possibility to circumvent the filtration step. Furthermore, under these conditions amino alcohol **3** is liberated from its adduct with the reducing agent. Unfortunately, using these alternative procedures the content of the amino alcohol in the crude product decreased dramatically thereby outweighing the advantages mentioned above. In addition, the extraction of the amino alcohol from the aqueous phase during workup had to be investigated as well. **3** was found to be sufficiently soluble in ethyl acetate. However, by using this solvent, byproducts of the reaction, which were not analyzed, were also extracted, leading to lower product purity and lower yield after crystallization. TBME extraction was examined, but problems with phase separation were encountered. This might be due to the presence of trichloro ethanol which is formed by reduction of trichloro acetic acid—the acid component applied in this particular case. By using trifluoroacetic acid the corresponding alcohol does not interfere with the workup procedure, and the desired product is obtained in higher yield. The reason for this observation was not investigated in detail. The best results in terms of both yield and product purity could be achieved by extraction of **3** with dichloromethane or chloroform although long extraction times were needed due to the reduced solubility of the product as compared to, for example, solubility in ethyl acetate.

Crystallization experiments for final purification of **3** revealed ethyl acetate to be slightly superior to TBME.

By applying the optimized procedure (*R*)-2-amino-1-(2-furyl)ethanol (**3**) was obtained in 64% yield with a purity greater than 99% and an enantiomeric excess over 99.5%. **3** was analyzed by GC after transformation of the amino alcohol into the corresponding acetonide with acetone/sulphuric acid and by GC/MS after silylation with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide.

Production of (*R*)-2-Amino-1-(2-furyl)ethanol (3) on Kilogram Scale. For up-scaling of the procedure no significant changes of the laboratory process were necessary. For the *Hb*HNL-catalyzed cyanohydrin reaction (synthesis of **2**) a cooled reactor, operated atmospherically under N_2 purging, was charged with TBME and freshly distilled furan-2-carbaldehyde (**1**). After cooling to 0°C the enzyme solution [diluted with K_2HPO_4 buffer (pH 5.2) and adjusted to pH 4.9 with a 10% citric acid solution] was added. The mixture was stirred for 10 min at 0 °C. During 45 min of HCN dosage the temperature was kept below 3 °C. The remaining HCN from the pump vessel was fed into a HCN-killing drum containing a NaOH solution. The reaction was stirred at 0°C and monitored by GC. When the conversion of the aldehyde exceeded 99%, a filter aid and TBME were added to the reactor; after 5 min the reaction mixture was pressed over a precoated filter with N_2 pressure. After phase separation the organic phase was stabilized with citric acid. The aqueous phase was washed twice with TBME (also used for precoating of the filter and washing of the filter cake), and the combined organic solvents and residual water were removed in a film evaporator yielding pure (*R*)-2-(2-furyl)-2-hydroxyacetonitrile (**2**). Unreacted HCN in the water phase was destroyed with a NaOH solution and iron sulphate. The required amount of **2** was produced in six consecutive batches in a fully reproducible way (Table 2. The reduced yield in the first batch was due to bad phase separation. This problem could be overcome by addition of larger amounts of filter aid to minimize the solvent interphase).

Table 2. **Synthesis of (*R*)-2-(2-furyl)-2-hydroxyacetonitrile (2) on kilogram scale**

batch	quantity [kg]	yield [%]	ee [%]	batch	quantity [kg]	yield [%]	ee [%]
1	0.69	56	99.1	4	1.10	90	99.3
2	1.03	84	98.8	5	1.13	92	99.0
3	1.11	90	99.3	6	1.16	95	99.4

The combined cyanohydrins **2** were subjected to reduction in two batches. Sodium borohydride was added to a reactor containing THF. Subsequently, trifluoroacetic acid was added slowly over a period of 60 min. After an additional 15 min of stirring, a solution of **2** in THF is added dropwise over a period of 90 min. Both the addition of trifluoroacetic acid and **2** are exothermic and cause hydrogen formation. The reaction was finished after approximately 2 h. The resulting suspension was dropped slowly into water, again conceivably an exothermic step. From the start the temperature was kept between 15 and 25 °C. Stirring was continued until the gas development had ceased. After the addition of a filter aid and filtration and washing of the precipitate with THF, the latter was removed from the filtrate in vacuo. The residual water phase was adjusted to pH 2 with 6 M HCl and was stirred overnight and washed with dichloromethane. In the following step the pH was shifted to 13−14, and the product was extracted with dichloromethane in a continuous fashion. Finally, the raw material was recovered after drying of the combined organic extracts by azeotropic distillation, polish filtration, and complete removal of the solvent. Recrystallization from ethyl acetate furnished amino alcohol **3** with a yield of 57%.

In summary, we provided a synthetic route for the production of (*R*)-2-amino-1-(2-furyl)ethanol (**3**) via biocatalytic hydrocyanation of furan-2-carbaldehyde (**1**) and subsequent reduction of (*R*)-2-(2-furyl)-2-hydroxyacetonitrile (**2**) with sodium borohydride. **3** was obtained with higher

than 99.5% enantiomeric excess and with a purity greater than 98%, completely meeting the required specifications. The described procedure constitutes an efficient method for the stereoselective chemoenzymatic large-scale production of chiral 1-substituted ethanol amines. Furthermore, it also grants access to products bearing substitution patterns other than the furyl moiety and presumably with both (*R*)- and (*S*)-configuration.

Experimental Section

General. All reagents and solvents were obtained from commercial sources and appropriately purified if necessary. Due to the limited stability of cyanohydrin **2**, prolonged storage should be avoided. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 Avance Series. For GC and GC/MS analyses see below.

HCN: Safe Handling. Hydrocyanic acid was produced in the HCN plant at DSM. It is important to avoid contamination either by base, which could lead to violent polymerization, or by strong acids, which results in formation of gaseous products.[16] Residual hydrocyanic acid from the HCN dosage line and unreacted HCN in the aqueous phase of the reaction mixture were destroyed in a diluted NaOH solution.

(*R*)-2-(2-Furyl)-2-hydroxyacetonitrile (2): Laboratory Procedure. 1 (28.8 g, 0.30 mol) was dissolved in 85 mL of TBME and cooled to 0 °C. *Hb*HNL solution (7.0 mL, 6500 iU/mL, determined for cleavage of mandelonitrile) was diluted with 128 mL of phospate buffer pH 5.2 (50 mM), and the pH was adjusted to 4.9 with a 10% citric acid solution. The phases were combined in the reactor and stirred at 0 °C until an emulsion was formed. HCN (29.3 mL, 0.76 mol) was added over a period of 15 min. After 2.5 h the reaction mixture was diluted with 100 mL of TBME and was filtrated over Celite. The Celite was washed with 50 mL of TBME. After phase separation the aqueous phase was extracted with TBME (2 × 60 mL), and the combined organic phases were dried with Na_2SO_4. Removal of the solvent furnished **2** as a slightly yellow oil in 83−95% yield and an ee > 99.5%. GC analysis: derivatization: 30 μL of cyanohydrin, 1 mL of CH_2Cl_2, 40 μL of pyridine, 47 μL of acetic anhydride, 3 drops of DMAP (10% solution in CH_2Cl_2), allowed to stand for 10 min. The ^{1}H- and ^{13}C NMR spectra of the racemic **2**-acetate used as a reference were consistent with literature data.[9a,17] Chirasil-DEX CB, 130 °C, 74 kPa H_2; retention times: 1.46 min **1**, 2.92 min *S*-**2** acetate, 3.36 min *R*-**2** acetate.

(*R*)-2-Amino-1-(2-furyl)ethanol (3): Laboratory Procedure. THF (900 mL) was placed in the reactor under a nitrogen atmosphere at 20 °C. $NaBH_4$ (55.3 g, 1.46 mol) was added slowly, and the temperature of the stirred slurry was adjusted to 15 °C. Subsequently, 166.6 g (1.46 mol) of trifluoroacetic acid was added slowly (H_2-development) over a period of 60 min, while the temperature was kept between 15 and 22 °C. After stirring for an additional 15 min 90.0 g (0.73 mol) of **2** dissolved in 100 mL of THF was added over a period of 90 min, keeping the temperature below 25 °C. The reaction mixture was stirred overnight. For workup 500 mL of water were added at 18 °C (H_2-development), and the reaction mixture was stirred until the gas development had ceased. After filtration of the white precipitate over Celite and washing with 100 mL of THF, the combined liquids were subjected to a distillation to remove THF. The residual aqueous solution was acidified with HCl (pH 2), stirred overnight, and extracted with CH_2Cl_2 (2 × 250 mL). By adding a 50% NaOH solution the aqueous phase was adjusted to pH 13−14 and extracted with CH_2Cl_2 in a continuous fashion. Drying of the combined organic phases with Na_2SO_4, filtration, and removal of the solvent under reduced pressure yielded 59.27 g of **3** as a yellow solid, yield 64%, ee >99.5%. A 35 g sample of raw **3** was recrystallized from ethyl acetate to yield 28 g of pure product (>99% purity). ^{1}H NMR (CD_3CN): δ = 2.43 (br s, 3H), 2.82 (dd, J = 13 Hz, J = 7 Hz, 1H), 2.91 (dd, J = 13 Hz, J = 5 Hz, 1H), 4.49 (dd, J = 7 Hz, J = 5 Hz, 1H), 6.25 (d, J = 3 Hz, 1H), 6.35 (dd, J = 3 Hz, J = 2 Hz, 1H), 7.42 (d, J = 2 Hz, 1H). ^{13}C NMR (CD_3CN): δ = 46.8, 68.9, 106.4 110.6, 142.3, 157.0. GC analysis: derivatization: 50 mg of **3**, 1 mL of acetone, 10 μL of H_2SO_4, allowed to stand for 15 min; Chirasil-DEX CB, 90 °C, 74 kPa H_2; retention times: 1.65 min *S*-**3** acetonide, 1.85 min *R*-**3** acetonide. GC/MS analysis: derivatization: 100 mg of **3**, 100 μL of *N*,*O*-bis(trimethylsilyl)-trifluoroacetamide in CH_2Cl_2; HP-5 column, 50 °C/2 min − 10 °C/min to 320 °C − 5 min, 66 kPa He; retention times: 10.92 min bis-silyl-**3**, 13.78 min trisilyl-**3**.

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